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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/691,237	10/19/2000	David S. Wells	085747/0170	5026

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/691,237	WELLS ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,37-42,44-55 and 57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,37-42,44,46-55 and 57* is/are rejected.

7)☒ Claim(s) *45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 35-42, 44-55 and 57 are pending.

The amendment presented on 9-30-05 has been entered.

Upon careful consideration the finality of the rejection of the last Office action has been withdrawn and the following rejection is applied to the pending claims.

Claim Rejections - 35 USC § 112

1. Claims 51-55 and 57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preparing the instant claimed composition so as to achieve the desired plasma concentrations of the drug upon administration, does not reasonably provide enablement for providing a treatment of the claimed pathological conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: breadth of the claims; nature of the invention; state of the prior art; amount of direction provided by the inventor; the level of predictability in the art; the existence of working examples; quantity of experimentation needed to make or use the invention based on the content of the disclosure; and relative skill in the art. All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

The breadth of claims: Instant claims are directed to a method of treating a pathology that is ameliorated by the modulation of CNS activity. Independent claim 51 recites the pathological conditions as a markush that includes spasticity, mood disorder, headache, neuropathic pain syndrome, cerebral trauma etc.

The nature of the invention: The invention is drawn to an oral sustained-release composition comprising a core matrix comprising a therapeutically effective amount of an active agent selected from the markush list and a gelling agent. Instant invention also describes that the claimed compounds are useful for treating CNS abnormalities such as epilepsy. The rejected claims 51-55 and 57 are drawn to a method of treatment as described above, employing the said composition.

The amount of direction provided by the inventor: Instant specification describes production of the composition i.e., the various active agents, percentages of the active agents in the composition including the proffered percentages that are also claimed.

The presence or absence of working examples :Instant specification describes the preparation of core matrix comprising active agent, a gelling agent such as xanthan gum and coating the active agent core with a film coating (see examples). The specification also provides the in vitro and in vivo dissolution profiles of the compositions.

However, instant specification does not provide any data on the efficacy of the above formulations in treating any of the claimed pathological conditions. In

particular, the claimed pathological conditions recite several conditions such as headache, substance abuse, and restlessness syndrome, cerebral trauma, all of which may or may not be related. Instant specification does not provide any guidance to as to preparing the compositions with an effective amount of the active for all of the above conditions nor provide any correlation between the composition and the release profiles shown with that of the claimed conditions. Thus, a skilled artisan would not be able to readily understand if the compositions described would be able to provide an effective therapy for the claimed conditions and therefore would turn to trial and error experimentation in order to be able to treat the claimed conditions.

The quantity of experimentation: In the instant case, the method claimed also recites a proviso that when certain compounds are being used, the pathology being treated is not convulsions. Instant specification does not provide any guidance as to which active agent in the composition, either as a simple matrix or a coated composition provides an effective treatment for the claimed diseases. Moreover, instant claims also recite multiparticulate compositions, which further proves to be burdensome for one of an ordinary skill in the art to determine as to which active agent could be used in a particulate form, coated or uncoated form, in order to treat a particular condition claimed. Consequently, a skilled artisan would have to turn to trial and error in order to be able to treat the claimed conditions in the absence of any guidance because the specification does not describe which type of active agent (among those claimed) in the

different types of compositions described provides an effective therapy for a particular condition.

The relative skill of those in the art: the skill of one of ordinary skill in the art is very high, e.g., Ph.D. and M.D. level technology.

Claim Rejections - 35 USC § 103

2. Claims 35, 37-39, 41, 42, 47, 51-54 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/44623 (WO) in view of Hsiao US 4,571,333 (Hsiao).

Hsiao teaches sustained release formulations comprising naproxen and naproxen salts in the form of oral tablets suitable for once-daily administration. The naproxen composition of Hsiao is made of a matrix composition 81-96% % by weight of naproxen and 4-9% by weight of hydroxypropyl methylcellulose and other excipients (examples, col. 4, lines 59-68 and col. 5, lines 1-4). Hsiao does not teach the claimed active agents.

WO teaches compositions comprising valerian extracts, isovaleric acid and their derivatives in combination with non-steroidal anti-inflammatory compounds such as naproxen, ibuprofen etc (page 14-page 17). Isovaleric acid and other valerian extracts taught by WO read on the instant claimed active agents. WO further teaches that the oral isovaleramide or valerian extract containing compositions, together with anti-inflammatory compounds can be prepared in the form of enteric-coated tablets, capsules etc., so as to successfully treat muscular aches, pain, as well as inflammation. WO fails to

teach a gelling agent or matrix formulation for the above active agents. However, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to prepare the composition of WO containing isovaleramide, isovaleric acid or valerian extracts and anti-inflammatory agents such as naproxen in the form of an oral sustained release matrix by adding a sustained release swelling agent, HPMC, because Hsiao teaches that the pain or inflammation treating composition prepared in a matrix with HPMC prolongs the release of the active agent so as to achieve a once-a-day administration. Alternatively, it would have been obvious for a skilled artisan at the time of the instant invention to add valerian extracts, isovaleramide etc. to the anti-inflammatory naproxen containing composition of Hsiao because WO suggests that the combination treats inflammation as well as provides a relief from acute pain and muscular tension. With respect to the claimed weight percentage, WO teaches upto 600 mg of active ingredient per tablet and further, the percentages of active ingredient and HPMC taught by Hsiao are within the claimed ranges. With respect to the process of preparing the composition, Hsiao teaches the same steps of mixing the ingredients, extruding and compressing to form tablets (col. 7). Accordingly, optimizing the amount of drug and the release agent, as well as choosing an appropriate release agent so as to achieve the desired release rate are within the scope of a skilled artisan.

3. Claims 40, 44, 46, 48-50 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO in view of Hsiao as applied to claims 35, 37-39, 41,

47, 51-54 and 57 and further in view of Groshovy et al (Groshovy, submitted on PTO-1449).

Hsiao and WO, discussed above, fail to teach a film coating that retards the access of the liquids to the active compounds.

Groshovy teaches coating of tablets with intestine soluble film forming polymer such as acetylphthalylcellulose so as to enhance the physical strength and resistance to the action of gastric juice (page 1). Groshovy teaches tablets containing valerian extracts are usually destroyed by gastric juices in two hours and the resulting weight loss prompts the addition of plasticizers to the film-forming substances (page 4). Therefore, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to employ a film-forming coat over the oral composition of WO containing valerian extracts and anti-inflammatory such as naproxen in the form of a sustained release matrix containing HPMC (the sustained release agent of Hsiao) because Groshovy teaches that tablets containing valerian extracts are sensitive to gastric juices and a film-forming polymer together with a plasticizer reduces the sensitivity of the composition to gastric juices and the plasticizer enhances the strength of the film surrounding the composition.

Response to Arguments

Applicant's arguments filed 1-31-06 have been fully considered but they are not persuasive.

Applicants argue that it was applicants who first recognized that the claimed isovaleramide, isovaleric acid, and the other related compounds have a short half-life in vivo as set forth in example (pages 2 and 5 of the specification) and there was no motivation in the prior art to provide the recited compounds in a sustained-release composition.

Applicants agree that Hsiao (USPN 4,571,333) is directed to sustained-release formulations of naproxen, an NSAID. Artman (WO 99/44623) is directed to combination therapies comprising the administration of isovaleramide (or related compounds) and an NSAID. However, they argue that this combination of references does not establish a prima facie case of obviousness of the instant claims, even though Hsiao shows a sustained-release formulation of another drug. It is argued Hsiao teaches away from modification of its invention because the objective of Hsiao is to provide a maximum amount of naproxen (500-1200 mg) in a tablet with minimum bulk and to achieve this goal, the tablets of Hsiao must contain from 81-96% by weight naproxen. This simply does not leave room for a therapeutically effective amount of the active compounds of the present invention. Applicants also argue that 40-70% w/w amount of active compound recited in the claims left no question that compositions based on Hsiao are excluded from the claims, because a composition cannot comprise both 81-96% naproxen and 40-70% w/w isovaleramide compound and that it would be

impossible to formulate a composition that comprises both 81-96% naproxen, as required by Hsiao, and 40-70% of the presently claimed active compounds.

Applicants' arguments have been considered but not found persuasive because while it is true that Hsiao teaches a large amount of naproxen, which would not allow any room to add the claimed active compounds, WO teaches (as admitted by applicants) the claimed compositions and also suggests combinations of isovaleramide and naproxen. Both WO and Hsiao are directed to an anti-inflammatory treatment with the drugs and Hsiao provides the required motivation to add HPMC as the matrix material in the composition of WO.
The combination of references is to show that it would have been obvious for one of an ordinary skill in the art to add HPMC of Hsiao to the composition of WO containing isovaleramide because Hsiao teaches that the composition prepared in a matrix with HPMC prolongs the release of the active agent so as to achieve a once-a-day administration. With respect to the high amount of naproxen taught by Hsiao, the motivation is to add the HPMC of Hsiao and not naproxen of Hsiao. Further, WO teaches combination of drugs for the same purposes i.e., treating pain and inflammation and therefore, optimizing the amounts of individual active agents, drawn to treat the same conditions so at to achieve an additive, if not a synergistic effect, depending on if one of an ordinary skill in the art chooses to use isovaleramide alone or isovaleramide in combination with naproxen.
With respect to providing sustained release compositions, Hsiao teaches sustained release compositions containing pain treating drugs and that HPMC enables a prolonged release of the drug, thus providing the required motivation

for a skilled artisan to prepare pain treating isovaleramide compositions in a sustained release form.

Applicants' arguments with respect to the claimed amounts of drugs have been considered. However, examiner notes that on page 11 of the specification, the claimed percentages are only exemplary and as explained above, one skilled in the art would be able to readily optimize the amounts of naproxen and the isovaleramide compounds when used in combination because both are used for the same purpose. Hsiao teaches that certain additives such as HPMC help achieve a sustained release of the drug to provide effective treatment.

With respect to the declaration provided, examiner finds that the declaration is not persuasive because it only provides facts that are not supported by any comparative data that allows the examiner to make any comparisons. Further, the declaration is also directed to specific ingredients and hence is not commensurate with the scope of the instant claims.

Allowable Subject Matter

Claim 45 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicants are requested to update the status of the co-pending application mentioned by serial numbers throughout the instant specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM - 6.30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lakshmi S Channavajjala
Examiner
Art Unit 1615
April 17, 2006

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